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REVIEW ARTICLE

The risk of intrauterine exposure to SARS-CoV-2 in female COVID-19 patients: A comprehensive review

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of coronavirus that has caused fatal infectious diseases and global spread. This novel coronavirus attacks target cells through the interaction of spike protein and angiotensin-converting enzyme II (ACE2), leading to different clinical symptoms. However, for a successful pregnancy, a well-established in-uterine environment includes a specific immune environment, and multi-interactions between specific cell types are prerequisites. The immune-related changes in patients infected with novel coronavirus could interfere with the immune microenvironment in the uterus, leading to fetal loss. We first reviewed the intrauterine environment in the normal development process and the possible pregnancy outcome in the infection state. Then, we summarized the immune response induced by SARS-CoV-2 in patients and analyzed the changes in ACE2 expression in the female reproductive system. Finally, the present observational evidence of infection in pregnant women was also reviewed.

KEYWORDS
angiotensin-converting enzyme 2, endometrium, fertility, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

It had been more than 1 year since China first reported a few cases of pneumonia of unknown cause. The pathogen was later identified as a new type of coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The coronavirus is spreading rapidly, and there is no sign of ending. SARS-CoV-2 infects and lysis the host cells by binding with angiotensin-converting enzyme II (ACE2), which is widely expressed in the ovary, uterus, vagina, and placenta.[2–5] However, whether SARS-CoV-2 would cause intrauterine infection or affect female fertility is still a mystery, which should not be neglected.

Researchers mainly pay attention to women in the second or third trimester of pregnancy and paid more attention to the evidence of the vertical transmission of SARS-CoV-2.[6,7] At present, there is little evidence that SARS-CoV-2 would spread vertically during the third trimester of pregnancy.[8–10] It was proved that most of the clinical symptoms of pregnant women infected with SARS-CoV-2 were not obvious.[10–12] However, the effect of SARS-CoV-2 on early pregnancy still lacks clinical evidence. Because the successful blastocyst implantation is closely related to the state of the endometrium and its acceptance time window, the establishment and maintenance of a normal pregnancy require sufficient crosstalk between the endometrium and the embryo and the embryo best microenvironment in uterus.[13–15] In addition, abnormal hormone and inflammatory environments may disturb the dialog of immune-endocrine interaction between the decidua and trophoblast during embryo implantation, leading to pregnancy complications.[16–19]

In this review, we would like to explain the risk of intrauterine exposure to the SARS-CoV-2 virus in female patients with COVID-19 and whether it could interrupt the development of pregnancy.

2 | NORMAL PREGNANCY REQUIRES A WELL-ESTABLISHED INTRAUTERINE ENVIRONMENT

Endometrial epithelial cells express estrogen and progesterone receptors, which can sense hormone changes and send signals to endometrial stromal cells and immune cells.[20] Endometrial stromal cells also express estrogen and progesterone receptors and experience decidualization under the stimulation of hormones. They can secrete cytokines and regulate the activity of immune cells.[20–22] During pregnancy, trophoblast cells and decidual cells secrete different chemokines to recruit immune cells from peripheral blood.[23,24] Decidual immune cells (DICs) participated in the formation of uterine spiral arteries.[25] the directional migration of trophoblast cells,[26] and protection of the fetus from infection.[27] Because the fetus is similar to a semiallograft, maintaining normal pregnancy requires DICs to form an immune tolerance microenvironment in the maternal interface to avoid the fetus's maternal immune rejection. For example, decidua natural killer Cells (dNK cells) show low-toxicity CD16 ^{dim} CD56 ^{high} phenotype.[28] Moreover, our previous studies confirmed that the decidual CD8$^+$ T cells highly expressed inhibitory receptors, such as PD-1 and Tim-3, and showed a highly exhausted phenotype, with low cytotoxicity.[29]

In addition, indoleamine-pyrrole 2,3-dioxygenase (IDO) derived from monocytes and FasL on the trophoblast surface could inhibit T cells' activity via different mechanisms.[30–32] Progesterone, which was sustained at a high plateau during pregnancy, can also inhibit the cytotoxicity of CD8$^+$ T cells.[33] Therefore, immune adaptability is required to adapt to the fetus. The special immune-microenvironment of the fetal-maternal interfaces may relate to the increased risk for acquiring infections, which have demonstrated that certain conditions disproportionately affect pregnant women.[34]

The dysfunction of the endometrium is one of the main causes of decreasing fertility. It was reported that about 60% of pregnancy loss occurs at 3–4 weeks during embryo implantation, and 10% occurs at 4–12 weeks of pregnancy.[35] Abnormal maternal-fetal interaction may cause spontaneous abortion in the first trimester of pregnancy, resulting in fetal growth restriction or eclampsia in the second or third trimester. The study of infection during pregnancy shows that various pathogens such as cytomegalovirus (CMV), dengue fever, acquired immunodeficiency syndrome, and rubella infections in early pregnancy would induce abortion.[36] Infection can lead to abnormal maternal-fetal interactions through various mechanisms. TNF-α is a critical effector to induced pregnancy loss because blockade of TNF-α or TNF-α deficiency is a protective effect against the antiphospholipid syndrome.[37] While pregnant mice were challenged with LPS, a cell wall component from gram-negative bacteria, the decidua can synthesize and secret TNF-α, which results in fetal resorption.[38] Injection of polyinosinic-polycytidylic acid (Poly(I: C)), a viral mimic, can lead to fetal death through NKG2D-dependent manner by uterine NK cells or through IFNAR expression in pregnant mice.[39,40] Meanwhile, we cannot neglect that pathogens could directly attack the trophoblast leading to fetal death. For example, CMV can target trophoblast cells, induce apoptosis of trophoblast cells, and activate TNF-α, leading to cell death and pregnancy failure.[41]

3 | THE TARGET OF SARS-COV-2 AND ITS PATHOGENESIS

SARS-CoV-2 mainly encodes four structural proteins named spike protein (S protein, composed of S1 subunit and S2 subunit), membrane protein, envelope protein, and nucleocapsid, respectively.[42] SARS-CoV-2 initiates the fusion of the viral envelope and cell membrane through the interaction between S protein and ACE2 receptor, and the viral genome is subsequently released to target cells.[43] Subsequently, the virus started to replicate and translate into the host cells. Single-stranded (ss) RNA-sensing Toll-like receptors (TLR), such as TLR3 and TLR7 in the endosome, could recognize SARS-CoV-2 virions. And then, the recognition could activate the interferon regulatory factor (IRF) 3, IRF7, and nuclear factor (NF) -$\varkappa$B, inducing fast production of IFN-I, IFN-III, and proinflammatory cytokine.[44] IFN-signaling plays a critical role in antiviral immune response.[45] However, the function of

more than a dozen of kinds of proteins encoded by SARS-CoV-2 is to escape immune recognition of host cells and killing.[46–48] For example, nonstructural protein 1 (NSP1) protein could inhibit host protein, thus inhibiting IFN-β production.[46] Based on immune escape mechanisms, severe patients usually show a delayed IFN reaction and prolonged virus replication.[49] Cytokine storm followed with impaired IFN response was another feature in coronavirus disease 2019 (COVID-19) clinical manifestation.[50,51]

After transcription factors such as NF-κB, c-Jun, and the downstream of p 38/MAPK (mitogen-activated protein kinase) pathway are activated, the levels of inflammatory cytokines including IL-6 and TNF-α are rapidly produced, resulting in the recruitment of macrophages, monocytes, DCs, and neutrophils to lung.[52–54] The pulmonary macrophages might fire the first shot in the process of antiviral immune. Single-cell RNA sequencing (scRNA-seq) from the bronchoalveolar lavage (BAL) of COVID-19 patients shows that macrophages and monocytes take a large proportion from the BAL of severe disease.[55] These inflammatory monocytes displayed a pro-IFN signature, which expressed chemokines such as CCL2, CCR5, and CXCR3 ligands and genes from IFN-stimulated genes, eventually forming a profibrosis differentiation pattern.[55]

ACE2 is widely expressed in the lung, cardiovascular system, intestine, kidney, central nervous system, and adipose tissue.[56] Although SARS-CoV-2 mainly targets alveolar cells, it can also impair organs outside the lungs and cause clinical symptoms whether the virus directly infects it or not.[57] Systemic inflammatory response syndrome (SIRS), or virus directly transmitting to organs through vascular transport and replicated in organs, is the cause of damage in distal tissues.[58,59] Clinical tests show that almost 40–80% of patients diagnosed as COVID-19 have elevated troponin-I levels, indicating myocardial injury.[60,61] Among men infected with SARS-CoV-2, different degrees of inflammatory changes can be found in testicular tissue, which expresses ACE2 in various types of cells with impaired sperm quality (Figure 1. A-B).[62–64] Recently, a preprint article revealed that the SARS-CoV-2 viral RNA was detected in 42.5% of reproductive tissues.[65] These pieces of evidence suggest that SARS-CoV-2 could target the reproductive system that expresses ACE2. However, there is insufficient research to provide substantial evidence for the harmful effects of this new virus on the reproductive system. Whether SARS-CoV-2 could also impair the female reproductive system was still a puzzle.[66]

4 | THE THEORETICAL BASIS OF INTRAUTERINE SARS-COV-2 INFECTION

It is reported that before pregnancy, the endometrial state of the women of childbearing age will change with the menstrual cycle. Castillo et al. analyzed the published endometrial transcriptome data, describing ACE2, TMPRSS, TMPRSS4, CTSB, CTSL, FURIN, MX1, and other primary gene expression levels in the endometrium. They found that the expression levels of TMPRSS4, CTSL, CTSB, FURIN, and MX1 were high, TMPRSS2 was medium, and ACE2 was low.[67] However, the expression of ACE2, TMPRSS4, CTSB, CTSL, and MX1 increased during the implantation window. In addition, the mRNA levels of ACE2, TMPRSS4, CTSB, CTSL, and MX1 genes increase with age.[67] It corresponded to the earlier research.[4] In our unpublished data, the expression level of ACE2 protein in decidual was higher than that in the proliferation stage. In addition, studies found that the RAS system was expressed in large quantities in the uterus, mainly containing target cells that encode ACE2.[4] A recent multicenter prospective study showed that 46.2% of women had abdominal or pelvic pain.[12] It cannot exclude the female reproductive system damaged in COVID-19 patients.

Whether pregnant women are harmed by SARS-CoV-2 infection is of interest to researchers and clinicians, especially in the context of a pandemic. After pregnancy, endogenous decidualization occurs in the maternal endometrial cells. Li et al. utilized the published maternal-fetal interface scRNA-seq to illustrate the dynamic levels of ACE2 at the maternal-fetal interface.[68] The results showed that ACE2 was highly expressed in the stromal cells, peridecidual cells, the placenta cytotrophoblast (CT) and syncytiotrophoblasts (SCT), while it was lower expressed in extravillous trophoblasts (EVT) and gradually increased with the development of embryo.[68] However, another team analyzed the published single cells data of early pregnancy and concluded that the maternal-fetal interface showed little susceptibility to infections of SARS-CoV-2 because compared to the expression levels of AXL, a receptor of Zika virus (ZIKV) which can be vertically transmitted from an infected mother to the developing fetus in utero, the expression level of ACE2 was lower.[69] In addition, the expression of ACE2 in placental gradually decreased with pregnancy.[70] These researches may partly explain why SARS-CoV-2 infections in the third trimester scarcely caused vertical transmission.[11]

5 | GESTATIONAL COMPLICATIONS AFTER SARS-COV-2 INFECTION

In the early period of the epidemic, due to the lack of a clear understanding of the pathogenic mechanism of SARS-CoV-2, most pregnant women chose cesarean section for delivery. By performing nucleic acid tests on the fetus, delivery placenta, and amniotic fluid of women with SARS-CoV-2 infection, researchers found little evidence of virus intrauterine infection.[10,71] A cohort study in the United Kingdom showed that about 5% of newborn babies were detected SARS-CoV-2 mRNA positive. Six were found positive for SARS-CoV-2 within 12 h after birth, which could not exclude the possibility of vertical transmission.[11] It is worth noting that compared with nonpregnant women, the proportion of pregnant women suffering from serious diseases is relatively higher.[71]

According to a case report, a 22-week pregnant woman diagnosed with COVID-19 had aborted, and the placenta was positive for the SARS-CoV-2 test (Figure 1. C-D).[72] Specifically, the placenta (3×10^7 virus copies/mg) and umbilical cord (2×10^3 virus copies/mg) were tested positive for SARS-CoV-2. The patient had typical symptoms of pre-eclampsia, accompanied by severe hypertension and abnormal coagulation. In addition, placental pathology showed that SARS-CoV-2

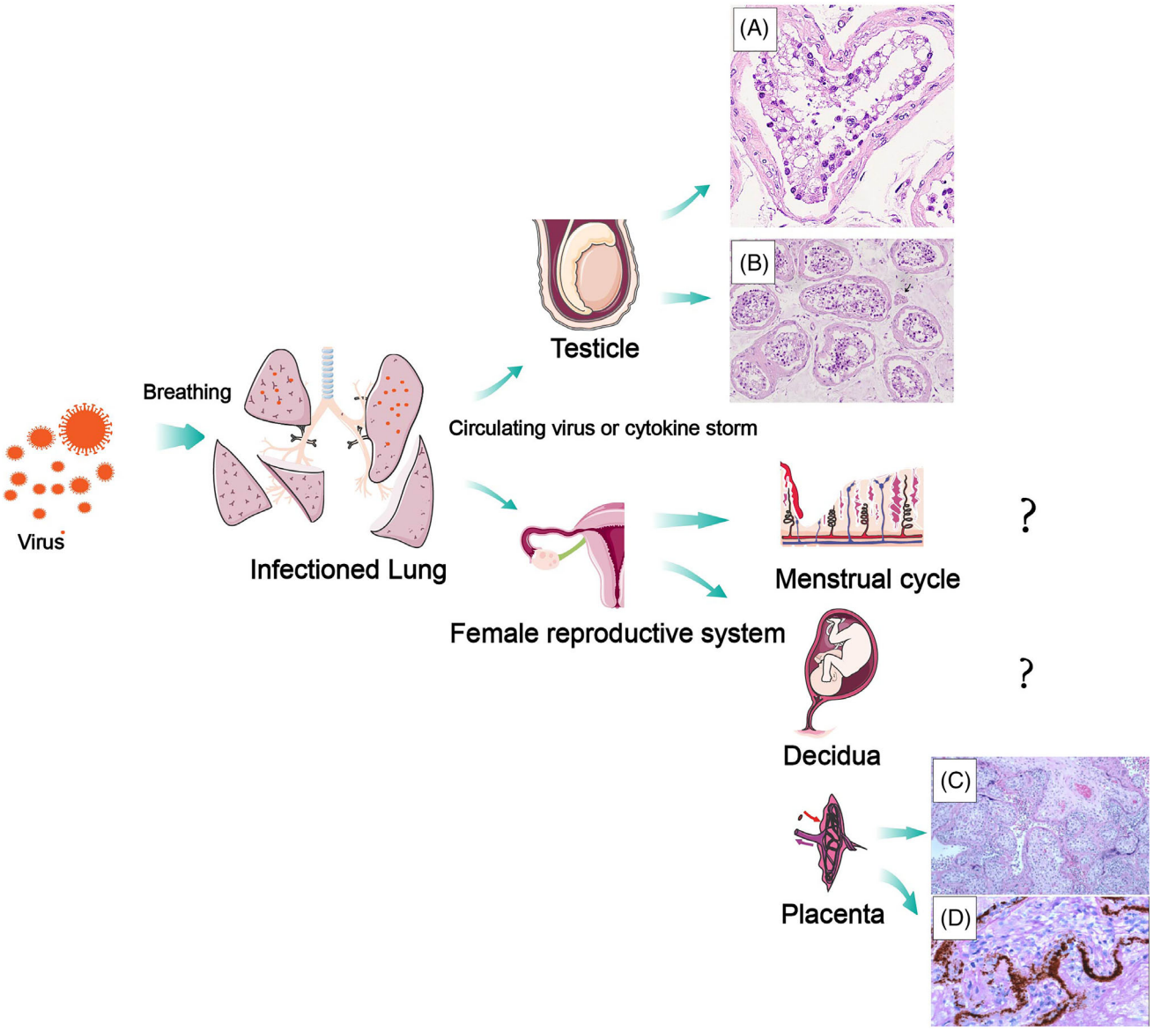

FIGURE 1 Illustrations of SARS-CoV-2 infection in the reproductive system. (A) Hematoxylin-eosin (HE) staining showed several pathological changes in the infected male testes[63]: Sertoli cells grow swelling, vacuolation, and cytoplasmic rarefaction, impaired spermatogenesis. (B) severe tubular injury shows cytoplasmic vacuolation and detachment of Sertoli cells from the basement membranes. Spermatogenesis is present. Scattered Leydig cells are present (arrow). However, few articles reported whether females' reproductive systems could be infected.[72] In infected pregnant women, HE staining images show histiocytic intervillositis at the section of the placenta. (C) In situ analysis for the presence of the virus, RNA confirms strong positive staining within the placenta. (D) The puzzles of whether endometrium or decidua could be infected need to be settled. The organ pictures were downloaded from the SERVIER MEDICAL ART (https://smart.servier.com/image-set-download/)

was mainly located in placental SCT, while fibrin deposition and mononuclear cell infiltrations were observed in the interstitial space, similar to lung pathology.[72] Another study reported the same clinical manisfication.[73] So far, more and more researchers have found cases of placental infection.[74–78] Recently, a multicenter clinical study demonstrated that pulmonary comorbidities, hypertensive disorders and diabetes were several risk factors for pregnant females developing severe complications of SARS-CoV-2 infection. Furthermore, the obstetrical and neonatal outcomes were determined by the maternal disease.[79]

Placenta infection by SARS-CoV-2 may not represent vertical transmission, but the severe placenta infections may hurt the nutrient exchange between fetal and decidua. Cribiù et al. found that more than half of pregnant women diagnosed with COVID-19's disease tested positive for placenta.[8] However, there was no evidence to show the relationship between the virus, placental pathology, maternal and perinatal outcomes.[8] The *Lancet* recently published an article reviewing the maternal and perinatal outcomes of the COVID-19 epidemic.[80] They found significant increases in stillbirth and maternal death during verses before the pandemic. However, there was no sig-

nificant change in the rate of premature delivery, while the incidence of ectopic pregnancies was increased.[80] Besides, there was no significant effect on pregnancy complications, such as maternal gestational diabetes, pregnancy-induced hypertension, and premature delivery.[80] Although there was no vertical transmission, an article reported that IFN-stimulating gene (ISG) and major histocompatibility complex gene were up-regulated in the umbilical blood mononuclear cells of the fetuses whose mothers were diagnosed as COVID-19.[81] In conclusion, though the transmissibility of SARS-CoV-2 is horrific, the fetal development in the mother's uterus was relatively secure. It might be owed to the maternal immunologic barriers.

6 | CONCLUSION

In summary, considering the expression of ACE2 and the discovery of virus particles in the placenta, the reproductive system, including the uterus and ovary, is more likely to be infected with SARS-CoV-2. Among the women diagnosed with abdominal pain or pelvic pain, 46.2% have the possibility of a pelvic infection,[12] which could be a vital signal for reproductive damage. For women infected with SARS-CoV-2, it remains a mystery how the immune system of pregnant women fights the virus and whether the viral infection fatally damages women's fertility. These questions need to be answered in the background of the COVID-19 epidemic.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

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